## REMARKS

Applicants note that the Amendment filed on December 20, 2002 (Paper No. 16) has been acknowledged and entered into the record. Upon entry of the present amendment, claims 9, 12-15 and 17-20 are pending. Claims 11 and 16 have been cancelled herein, and Applicants reserves the right to prosecute the cancelled subject matter, as well as the originally presented claims, in continuing applications. Claims 9, 12-15 and 18-20 have been amended herein. Support for the amendment to claim 9 is found in the claims as originally filed and in the specification, *e.g.*, at page 1, lines 18 and 24; at page 3, lines 25-28; at page 4, lines 22-26; at page 5, lines 18-20; and at page 6, lines 1-24. Claims 12-15 and 18-20 have been amended herein to ensure proper antecedent basis throughout the pending claims. Accordingly, no new matter has been added.

**Information Disclosure Statement**

Applicants note that the Information Disclosure Statement filed on July 18, 2001 (Paper No. 9) has been acknowledged and signed by the Examiner.

**Claim Rejections Withdrawn 35 U.S.C. §§ 102, 103**

Applicants note that the rejection of claims 9, 11, 14-16 and 25 under 35 U.S.C. § 102(b) as being anticipated by O'Leary *et al.* has been withdrawn "in view of the amendments and persuasive arguments set forth by the Applicant." (Office Action, page 2).

In addition, the rejection of claims 9 and 11-20 under 35 U.S.C. § 103(a) as being obvious over O'Leary *et al.* in view of Sheibani *et al.* and Streit *et al.* is withdrawn "in view of the amendments and persuasive arguments set forth by the applicant." (Office Action, page 2).

**New Grounds of Rejection – Claim Rejections Under 35 U.S.C. §§ 112, second paragraph**

Claims 9, 11-20 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. In particular, the Examiner has asserted that the terms "thrombospondin compound" and "inhibitor of DNA topoisomerase I" are "unclear as to which compounds and inhibitors" these terms refer. (Office Action, page 3).

Applicants note that claim 9 has been amended herein to recite a method of inhibiting tumor cell growth in a mammal by administering a composition that includes a thrombospondin polypeptide and an inhibitor of DNA topoisomerase I enzyme activity, wherein the thrombospondin polypeptide is thrombospondin-1 (TSP-1) or thrombospondin-2 (TSP-2) and the inhibitor of DNA topoisomerase I enzyme activity is a water soluble camptothecin compound. Thus, the pending claims are not directed to any thrombospondin compound or any inhibitor of DNA topoisomerase I. Rather, the pending claims are directed to a specific subset of thrombospondin polypeptides and inhibitors of DNA topoisomerase I. As such, Applicants contend that the metes and bounds of these claims are definite and clear. Applicants, therefore, request that the Examiner withdraw this rejection.

Claims 9 and 11-20 have also been rejected under 35 U.S.C. § 112, second paragraph as being incomplete for "omitting essential steps, such omission amounting to a gap between the steps." (Office Action, page 3). According to the Examiner, the omitted steps include "the recitation of how the inhibition of tumors are to take place." (*Id.*)

As discussed above, claim 9 has been amended herein to recite a method of inhibiting tumor cell growth in a mammal by administering a composition that includes a thrombospondin polypeptide and an inhibitor of DNA topoisomerase I enzyme activity, wherein the tumor cell is a colon tumor cell, wherein the thrombospondin polypeptide is thrombospondin-1 (TSP-1) or thrombospondin-2 (TSP-2) and the inhibitor of DNA topoisomerase I enzyme activity is a water soluble camptothecin compound, and wherein tumor growth is inhibited in the presence of the thrombospondin polypeptide and said water soluble camptothecin compound compared to in the absence of said thrombospondin polypeptide and said water soluble camptothecin compound.

In view of these amendments, Applicants request that the Examiner withdraw this rejection.

**New Grounds of Rejection – Claim Rejections Under 35 U.S.C. §§ 112, first paragraph**

Claims 9, 11-20 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. According to the Examiner, the specification "while being enabling for a method of inhibiting colon cancer tumor growth comprising the administration of water soluble camptothecin in conjunction with TSP-1 and/or TSP-2, does not reasonably provide enablement for a method of inhibiting any and all cancer cells or tumors comprising the administration of any

and all DNA topoisomerase I inhibitors and any and all thrombospondin compounds." (Office Action, page 3).

Claim 9 and its dependent claims (including claims 12-15 and 17-20) have been amended herein to recite methods of inhibiting tumor cell growth ina mammal by administering a composition that includes a thrombospondin polypeptide and an inhibitor of DNA topoisomerase I enzyme activity, wherein the tumor cell is a colon tumor cell, wherein the thrombospondin polypeptide is thrombospondin-1 (TSP-1) or thrombospondin-2 (TSP-2) and the inhibitor of DNA topoisomerase I enzyme activity is a water soluble camptothecin compound, and wherein tumor growth is inhibited in the presence of the thrombospondin polypeptide and said water soluble camptothecin compound compared to in the absence of said thrombospondin polypeptide and said water soluble camptothecin compound.

The Examiner has acknowledged that the instant specification is enabling for "a method of inhibiting colon cancer tumor growth comprising the administration of water soluble camptothecin in conjunction with TSP-1 and/or TSP-2." (Office Action, page 3). Accordingly, Applicants request that the Examiner withdraw this rejection.

**New Grounds of Rejection – Claim Rejections Under 35 U.S.C. §§ 103**

Claims 9, 11-15 and 19-20 have been rejected under 35 U.S.C. § 103(a) as obvious over WO 99/54445 to Joshi *et al.* ("Joshi") in view of O'Leary, Sheibani and Streit, which were all cited in the previous Office Action. On page 6 of the Office Action, the Examiner states:

> Joshi *et al.* disclose a method comprising the steps of administering a therapeutic gene that encodes an anti-angiogenic compound and DNA topoisomerase inhibitor. Joshi *et al.* do not specifically teach the type of anti-angiogenic compound nor do they teach the type of topoisomerase inhibitor. ... However, O'Leary *et al.*, Sheibani *et al.* and Streit *et al.* do teach the topoisomerase inhibitor, and the types of TSPs used.

According to the Examiner, "it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to inhibit tumor cell growth with a method of administering anti-angiogenic compounds and DNA topoisomerase inhibitors, because the basic method was already taught." (Office Action, page 7).

Applicants traverse the Examiner's characterization that Joshi describes "the basic method" of inhibiting colon tumor cell growth recited by the pending claims. As described

above, the pending claims have been amended herein to recite methods of inhibiting tumor cell growth in a mammal by administering a composition that includes a thrombospondin polypeptide and an inhibitor of DNA topoisomerase I enzyme activity, wherein the tumor cell is a colon tumor cell, wherein the thrombospondin polypeptide is thrombospondin-1 (TSP-1) or thrombospondin-2 (TSP-2) and the inhibitor of DNA topoisomerase I enzyme activity is a water soluble camptothecin compound, and wherein tumor growth is inhibited in the presence of the thrombospondin polypeptide and said water soluble camptothecin compound compared to in the absence of said thrombospondin polypeptide and said water soluble camptothecin compound. Thus, the methods of the claimed invention are directed to methods of administering a TSP-1 polypeptide and a camptothecin compound in combination.

Joshi, in contrast, describes methods of administering a nucleic acid encoding an anti-angiogenic compound and a cell-cycle blocker compound such as camptothecin. The Joshi reference describes improved expression of a therapeutic nucleic acid when co-administered to cells with a cell-cycle blocker to synchronize the target cells. Joshi fails to teach delivery of thrombospondin polypeptides, and there is no motivation to substitute polypeptides for nucleic acids, because the purpose of the cell-cycle blocker is to hasten translocation of nucleic acids to the cell nucleus for transcription (thereby avoiding exposure to cytosolic nucleases). Since degradation by cytosolic nucleases is not an issue for polypeptides, there is no motivation to combine the Joshi reference with any of the other cited references describing thrombospondin polypeptides.

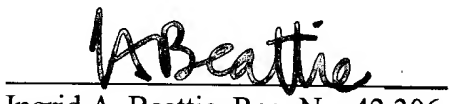
Therefore, the Examiner has failed to establish a *prima facie* case that one of ordinary skill in the art would have been motivated by the description in Joshi to modify the methods of administering a nucleic acid encoding a desired gene product to arrive at the claimed methods of inhibiting colon tumor cell growth by administering a combination of TSP-1 polypeptide and a camptothecin compound. Accordingly, this rejection should be withdrawn.

## CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

A petition for extension of time and a check in the amount of $465.00 is enclosed to cover the petition fee for a three month extension of time pursuant to 37 C.F.R. § 1.17(a)(3). The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 21486-038.

Respectfully submitted,



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